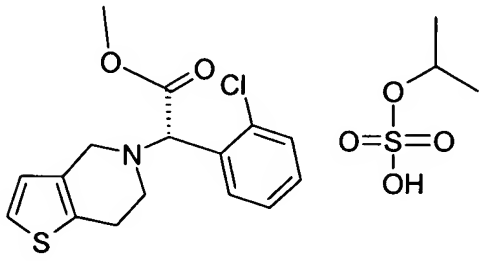
APPENDIX B

Process for the preparation of a salt of clopidogrel with isoproplyl-sulphate



In a boiling mixture of 22 ml of acetone and 20 ml of 2-propanol 3,0 g of clopidogrel hydrogensulphate of polymorph form 1 is dissolved. The mixture is slowly cooled to room temperature then kept in fridge overnight. The precipitated crystals filtered and washed with cold acetone.

Yield: 2.18 g (66%)

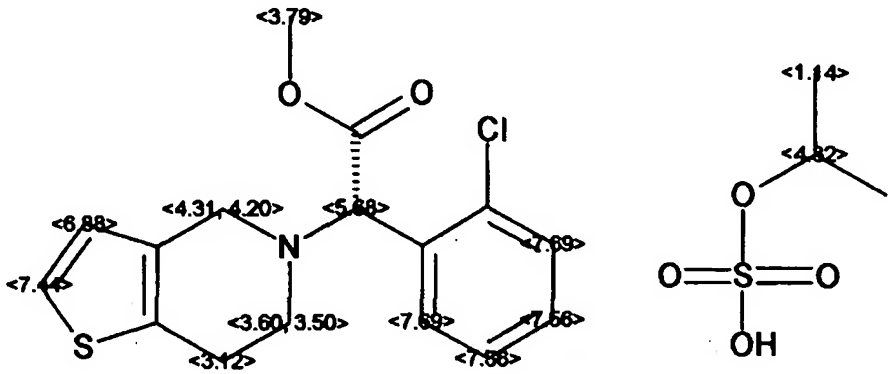
Analysis: $C_{19}H_{24}ClNO_6S_2$ (461.99)

Calculated: C 49.40 %; H 5.24 %; Cl 7.67 %, N 3.03 %, S 13.88 %
Found: C 49.30 %; H 5.31 %; Cl 7.82 %; N 3.19 %, S 14.01 %.

IR, ^{1}H-NMR and ^{13}C-NMR, X-ray diffractogram are enclosed

Leadási dátum:	2001.10.09.	mérések:	IR, HNMR, CNMR	Jegyzőkönyv:	IGEN
J.k. dátuma:	2001.10.11.	Mérések:	IR,HNMR,CNMR		

1H hozzárendelések:



DMSO+D2

13C (v. X) hozzárendelések:

IR (KBr): 3442, 1755, 1284, 1037.
HNMR (DMSO+D2O, i400): 7.69 (m, 2H), 7.56 (m, 2H), 7.44 (d, J=5.2 Hz, 1H), 6.88 (d, J=5.1 Hz, 1H), 5.68 (s, 1H), 4.32 (hp, J=6.2 Hz, 1H), 4.31 (d, 1H), 4.20 (d, J=14.7 Hz, 1H), 3.79 (s), 3.60 (m, 1H), 3.50 (m, 1H), 3.12 (m, 2H), 1.14 (d, J=6.3 Hz, 6H).
CNMR: 167.93, 134.94, 133.03, 132.21, 131.30, 130.71, 129.15, 128.67, 128.21, 125.99, 125.80, 69.98, 66.07, 54.39, 50.93, 49.78, 23.56, 22.78.

Jegyzőkönyv:

A spektrumok megfelelnek a fetételezett szerkezetnek. IPA hozzáadással bizonyítottuk, hogy a spektrumban látható 1 mol iPrO- csoport nem izopropanoltól származik.

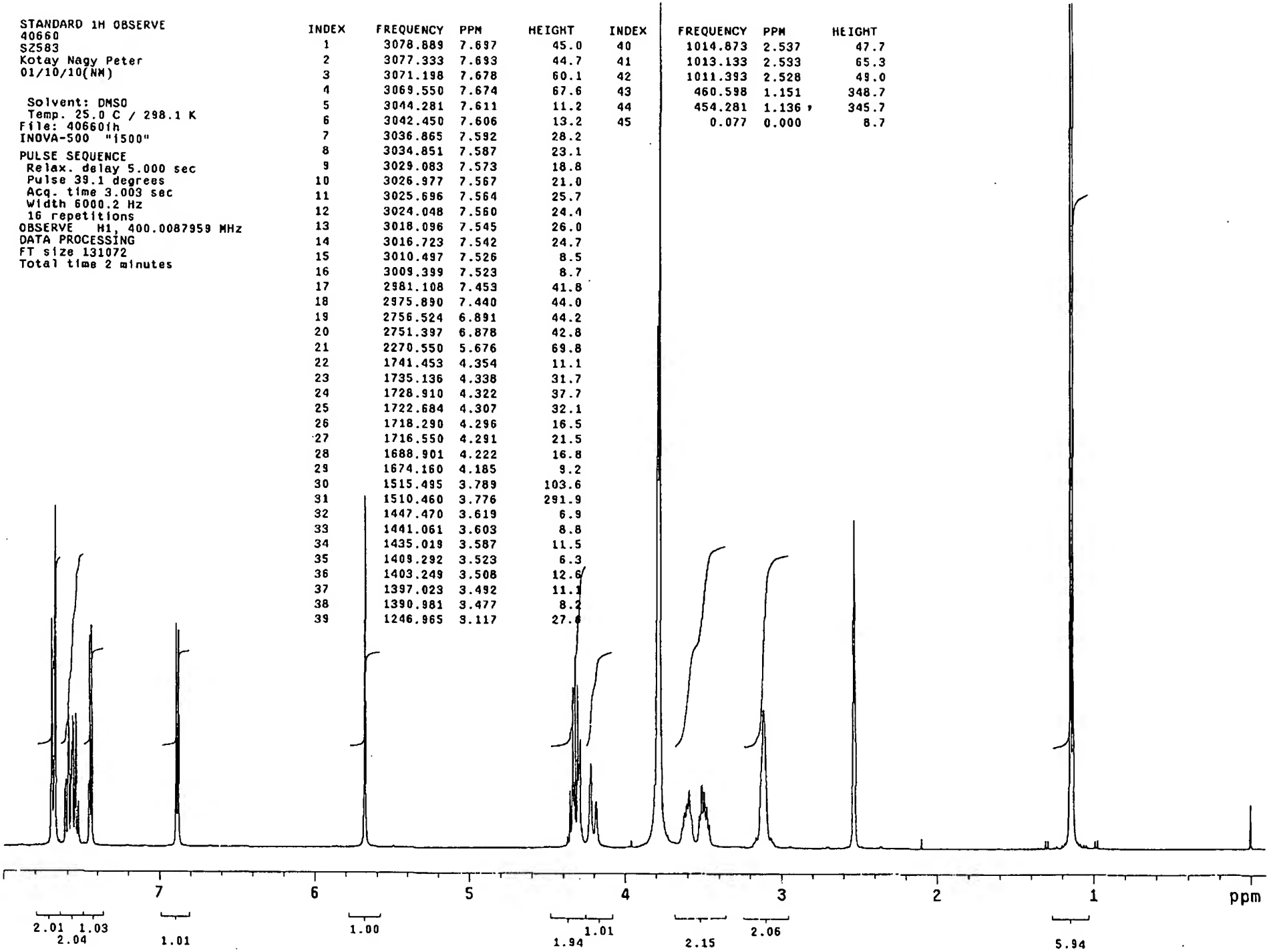
Dancsó András

STANDARD 1H OBSERVE
40660
SZ583
Kotay Nagy Peter
01/10/10(NM)

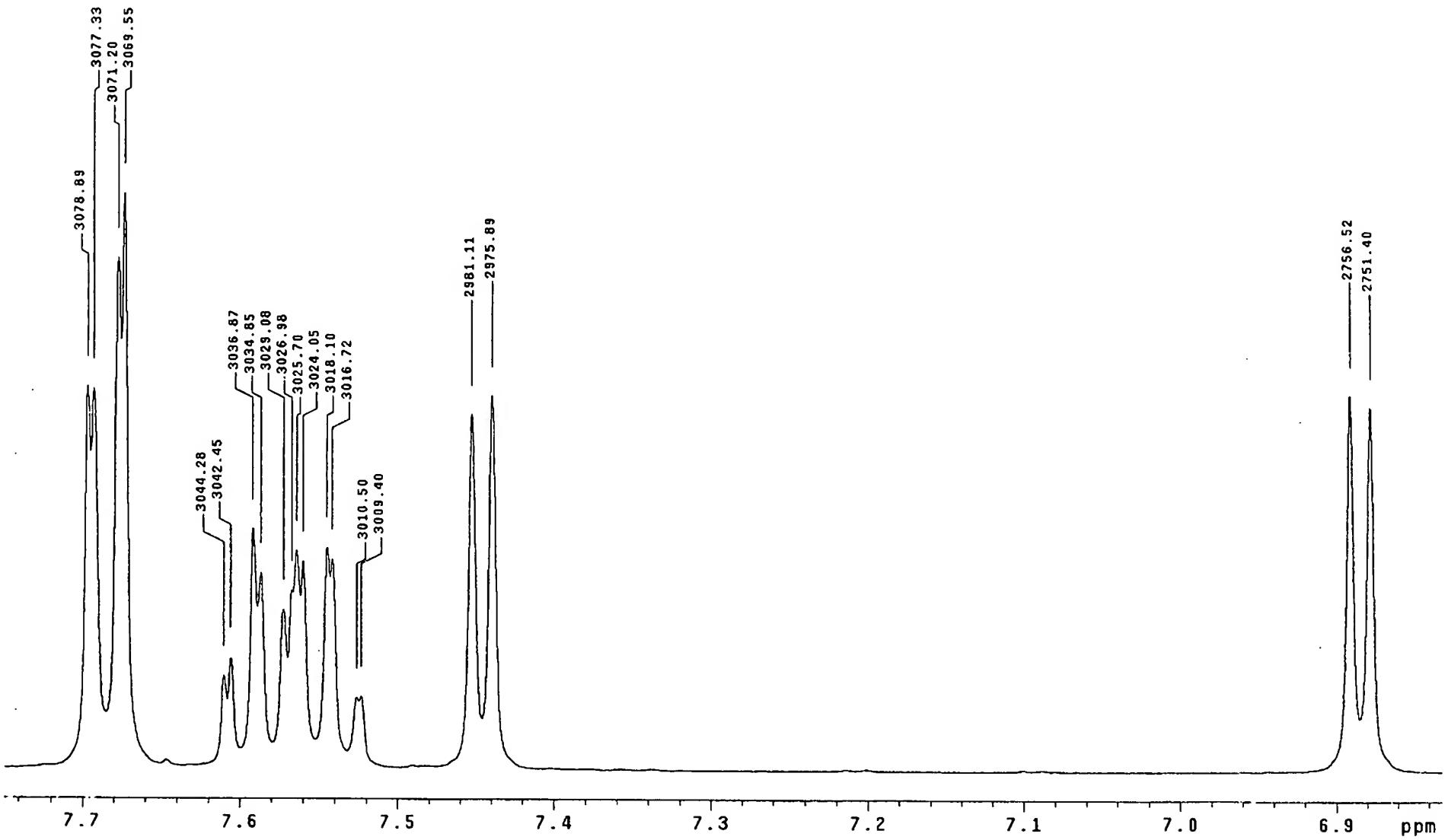
Solvent: DMSO
Temp. 25.0 C / 298.1 K
File: 40660fh
INOVA-500 "i500"

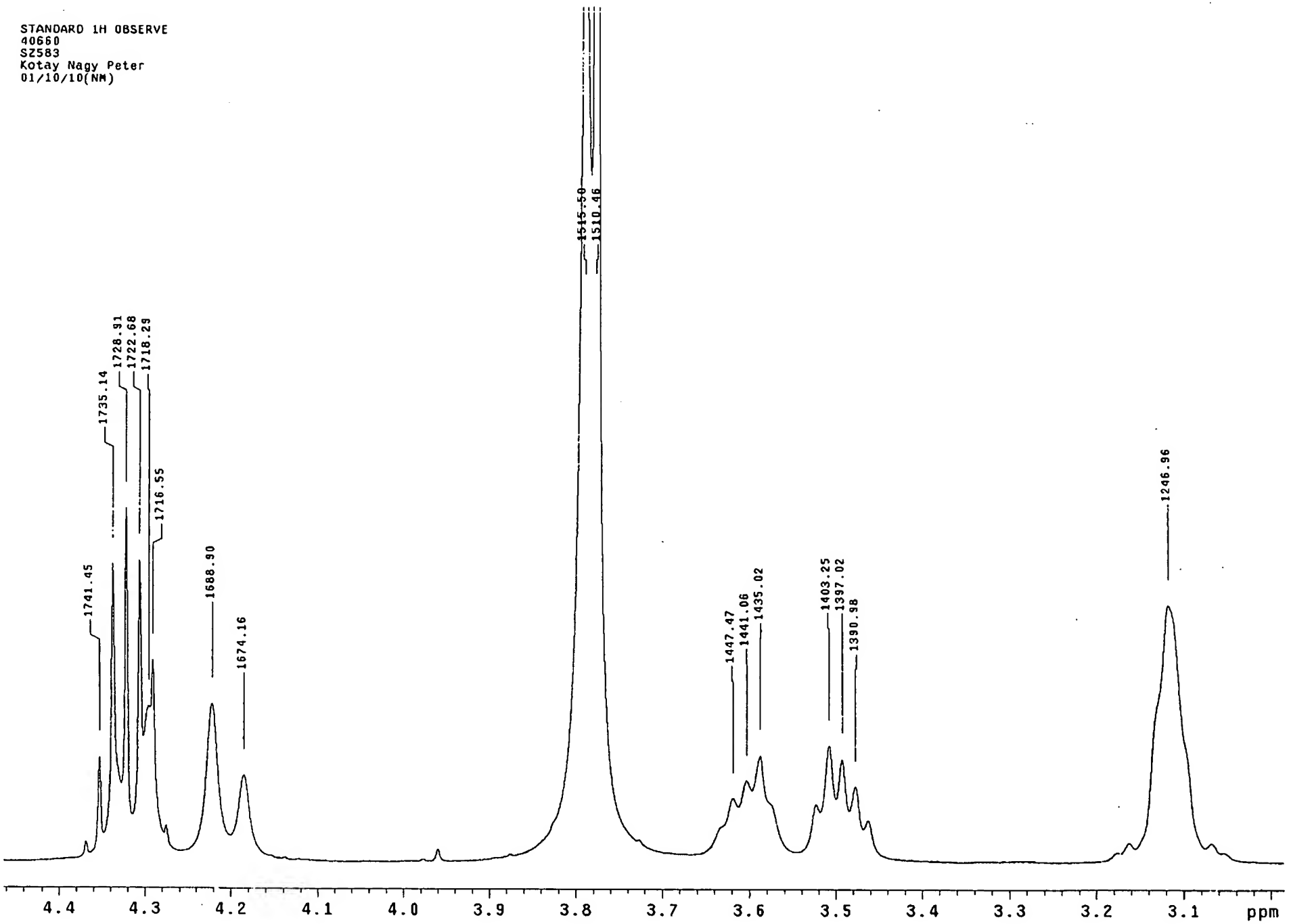
PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 39.1 degrees
Acq. time 3.003 sec
Width 6000.2 Hz
16 repetitions
OBSERVE H1, 400.0087959 MHz
DATA PROCESSING
FT size 131072
Total time 2 minutes

INDEX	FREQUENCY	PPM	HEIGHT
1	3078.889	7.697	45.0
2	3077.333	7.693	44.7
3	3071.198	7.678	60.1
4	3069.550	7.674	67.6
5	3044.281	7.611	11.2
6	3042.450	7.606	13.2
7	3036.865	7.592	28.2
8	3034.851	7.587	23.1
9	3029.083	7.573	18.8
10	3026.977	7.567	21.0
11	3025.696	7.564	25.7
12	3024.048	7.560	24.4
13	3018.096	7.545	26.0
14	3016.723	7.542	24.7
15	3010.497	7.526	8.5
16	3009.399	7.523	8.7
17	2981.108	7.453	41.8
18	2975.890	7.440	44.0
19	2756.524	6.891	44.2
20	2751.397	6.878	42.8
21	2270.550	5.676	69.8
22	1741.453	4.354	11.1
23	1735.136	4.338	31.7
24	1728.910	4.322	37.7
25	1722.684	4.307	32.1
26	1718.290	4.296	16.5
27	1716.550	4.291	21.5
28	1688.901	4.222	16.8
29	1674.160	4.185	9.2
30	1515.495	3.789	103.6
31	1510.460	3.776	291.9
32	1447.470	3.619	6.9
33	1441.061	3.603	8.8
34	1435.019	3.587	11.5
35	1409.292	3.523	6.3
36	1403.249	3.508	12.6
37	1397.023	3.492	11.1
38	1390.981	3.477	8.2
39	1246.965	3.117	27.6
40	1014.873	2.537	47.7
41	1013.133	2.533	65.3
42	1011.393	2.528	49.0
43	460.598	1.151	348.7
44	454.281	1.136	345.7
45	0.077	0.000	8.7



STANDARD 1H OBSERVE
40660
SZ583
Kotay Nagy Peter
01/10/10(NM)



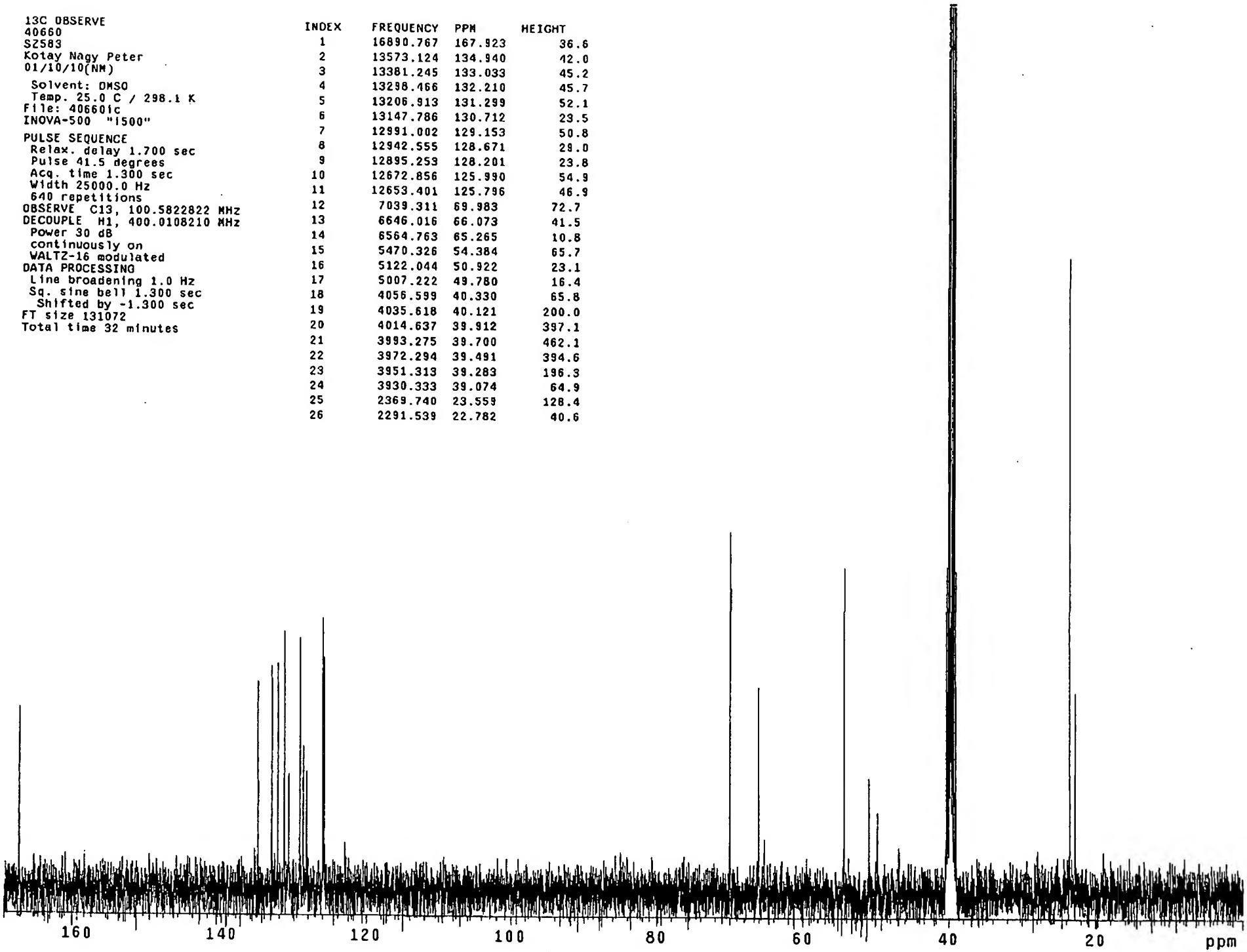

STANDARD 1H OBSERVE
40660
SZ583
Kotay Nagy Peter
01/10/10(NM)
1741.45
1735.14
1728.91
1722.68
1718.29
1716.55
1688.90
1674.16
1515.50
1510.46
1447.47
1441.06
1435.02
1403.25
1397.02
1390.98
1246.96
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
ppm

13C OBSERVE
40660
SZ583
Kotay Nagy Peter
01/10/10(NM)

Solvent: DMSO
Temp. 25.0 C / 298.1 K
File: 40660ic
INOVA-500 "I500"

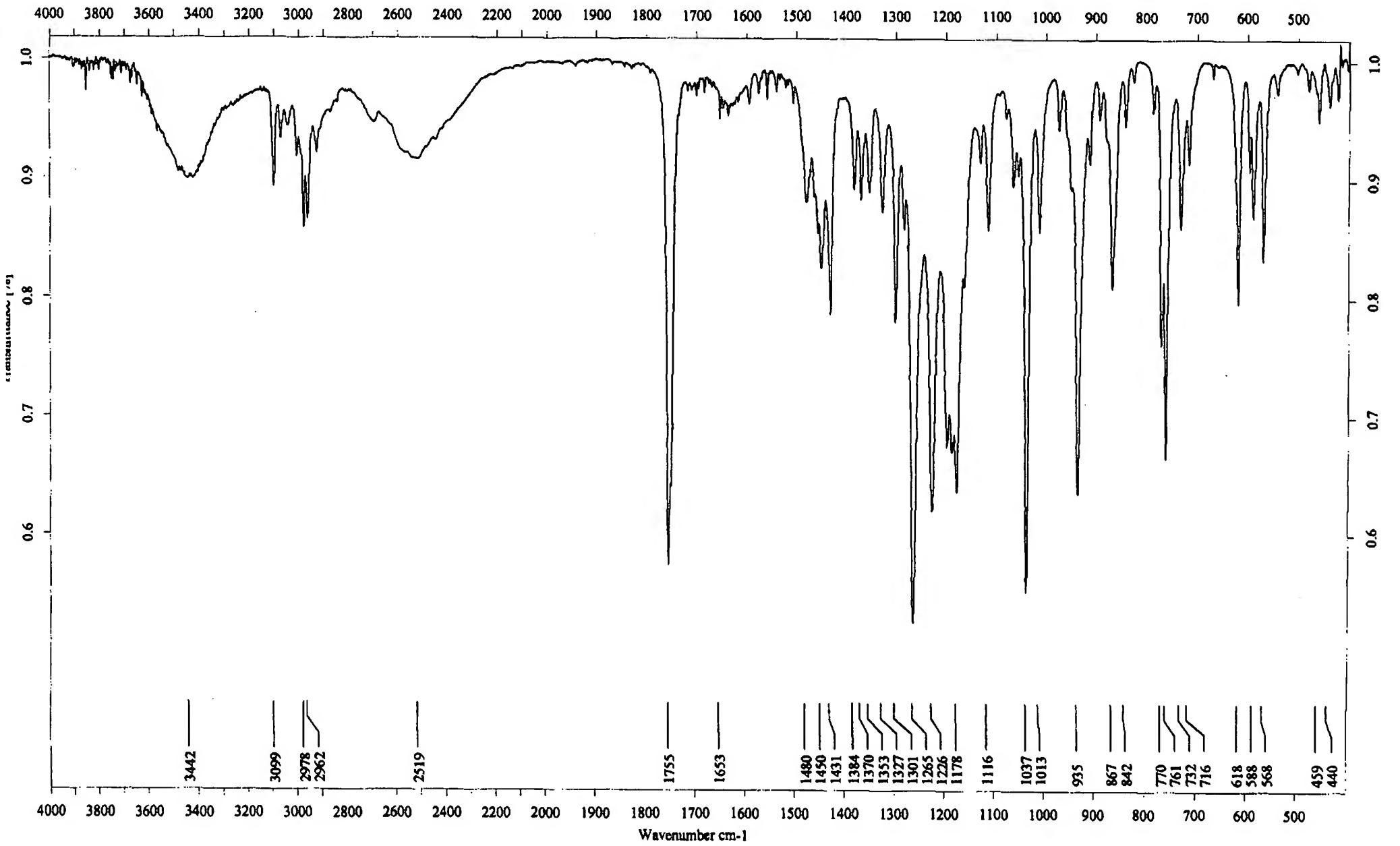
PULSE SEQUENCE
Relax. delay 1.700 sec
Pulse 41.5 degrees
Acq. time 1.300 sec
Width 25000.0 Hz
640 repetitions
OBSERVE C13, 100.5822822 MHz
DECOUPLE H1, 400.0108210 MHz
Power 30 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
Sq. sine bell 1.300 sec
Shifted by -1.300 sec
FT size 131072
Total time 32 minutes

INDEX	FREQUENCY	PPM	HEIGHT
1	16890.767	167.923	36.6
2	13573.124	134.940	42.0
3	13381.245	133.033	45.2
4	13298.466	132.210	45.7
5	13206.913	131.299	52.1
6	13147.786	130.712	23.5
7	12991.002	129.153	50.8
8	12942.555	128.671	29.0
9	12895.253	128.201	23.8
10	12672.856	125.990	54.9
11	12653.401	125.796	46.9
12	7039.311	69.983	72.7
13	6646.016	66.073	41.5
14	6564.763	65.265	10.8
15	5470.326	54.384	65.7
16	5122.044	50.922	23.1
17	5007.222	49.780	16.4
18	4056.599	40.330	65.8
19	4035.618	40.121	200.0
20	4014.637	39.912	397.1
21	3993.275	39.700	462.1
22	3972.294	39.491	394.6
23	3951.313	39.283	196.3
24	3930.333	39.074	64.9
25	2369.740	23.559	128.4
26	2291.539	22.782	40.6



0660	Kótay-Nagy Péter	MM
Z583	KBr	09/10/2001

BRUKER VECTOR22
Resolution: 2 cm-1
Number of Scans: 8



CLOPI18	Clopidogrel KF-69/16	04-04-20011.54186	Cu 40 30	0.04	4.5-34.9	1421
CLOPI22	Clopidogrel 1612 sz583	05-09-20011.54186	Cu 40 30	0.04	4.5-34.9	1962